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Review article

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Potassium and the kidney

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Abstract

In the past decade, understanding of the mechanisms by which the kidneys sense dietary potassium imbalance and affect the cardiorenal system has substantially advanced. These mechanisms explain why low-potassium diets promote salt-sensitive hypertension, whereas potassium-rich diets enhance natriuresis and lower blood pressure. Increasing dietary potassium may therefore be an effective strategy to reduce cardiovascular disease risk. Clinical trials have shown that replacing regular salt with potassium-enriched substitutes lowers blood pressure and reduces cardiovascular events and mortality. Emerging evidence suggests that low dietary potassium intake contributes to kidney injury, and low urinary potassium excretion is associated with accelerated chronic kidney disease (CKD) progression. However, whether the cardiorenal benefits of adequate potassium intake in CKD outweigh the risk of hyperkalaemia remains uncertain. A clearer understanding of the relationship between dietary potassium intake and blood potassium levels, as well as the optimal blood potassium range for kidney and cardiovascular health, is needed to resolve this question. New strategies to mitigate hyperkalaemia, including use of potassium binders and various kidney-protective drugs, could enable people with CKD to safely consume a potassium-rich diet and avoid the need to discontinue use of medications that increase the risk of hyperkalaemia, such as renin–angiotensin–aldosterone inhibitors and mineralocorticoid receptor antagonists.

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Key points

- The kidneys conserve potassium during times of deprivation and coordinates efficient kaliuresis following the ingestion of a dietary potassium load; renal K^+ handling also influences sodium reabsorption, so it has an important role in blood pressure regulation.
- The kidneys respond to changes in blood potassium levels via an indirect mechanism involving aldosterone and through direct potassium sensing via inwardly rectifying potassium channels.
- Hypokalaemia causes intracellular acidosis and ammoniagenesis in tubular epithelial cells, which promotes inflammation and impairs angiogenesis. This mechanism contributes to the development of tubulointerstitial fibrosis, hypoxic injury and hypokalaemic nephropathy.
- Adequate dietary potassium intake is associated with reductions in blood pressure, cardiovascular events and mortality, and may slow the progression of chronic kidney disease (CKD).
- Potassium-rich diets have little to no effect on blood potassium levels, whereas potassium-enriched salt substitutes or potassium supplements can increase blood potassium levels, with the extent depending on age, kidney function and use of medications.
- In patients with CKD, the risk of hyperkalaemia often leads to underuse or discontinuation of renin–angiotensin–aldosterone system (RAAS) inhibitors and mineralocorticoid receptor antagonists (MRAs) and restriction of dietary potassium; potassium binders, SGLT2 inhibitors and GLP1 receptor agonists reduce this risk and so may enable these patients to benefit from RAAS inhibitors, MRAs and a potassium-rich diet.

Introduction

Potassium (K^+) has been described as 'the cation of life' owing to its abundant intracellular concentration and essential role throughout evolution, from the earliest protocells — the precursors to life — to modern humans[1]. Nearly four billion years ago, protocells evolved in a potassium-rich environment, leading to high intracellular potassium concentrations that were essential for protein translation and cellular replication[2]. The subsequent development of ion-tight membranes and membrane pumps in aquatic unicellular organisms enabled them to survive in a sodium-rich extracellular environment and made intracellular potassium indispensable for maintaining membrane potential and cell volume[3].

As life transitioned to land, new selective pressures drove the evolution of the renin–angiotensin–aldosterone system (RAAS) and the ability of the kidneys to regulate potassium homeostasis[4]. In early hominins, the kidneys and endocrine system adapted to diets rich in fruits, roots, legumes and nuts, which are naturally high in potassium. These diets resulted in daily potassium intakes of up to 400 mmol/day (15.6 g/day), while sodium intake remained low (<50 mmol/day, <1.1 g/day)[5,6]. Thus, the nutritional potassium needs of modern humans have been shaped by millions, if not billions, of years of evolutionary pressure[6].

Unfortunately, the contemporary human diet differs markedly from the Palaeolithic diet, favouring sodium-rich, potassium-poor processed foods. As a result, in the USA and globally, the estimated average individual consumption of potassium is 54–66 mmol (2.1–2.6 g) per day, while sodium intake has risen to approximately 150–260 mmol (3.4–6.0 g) per day[7,8]. These intakes represent a reversal of the ancestral potassium-to-sodium (K^+ to Na^+) ratio from 8:1 in Palaeolithic diets to about 1:3 in current diets[9,10]. Humans are the only free-living, non-marine mammals that consume more dietary sodium than potassium[6]. This profound dietary mismatch between our evolutionary genome and the modern food environment has been linked to a range of adverse health outcomes, including salt-sensitive hypertension, cardiovascular disease, chronic kidney disease (CKD) and increased mortality[10]. In the past decade, both hypertension and suboptimal diets have surpassed tobacco as global leading risk factors for morbidity and mortality[11,12].

For decades, potassium has been recognized as a natural diuretic that counteracts salt-sensitive hypertension. In 1976, Meneely and Battarbee observed that "The high sodium-low potassium environment of civilized people, operating on a genetic substrate of susceptibility, is the cardinal factor in the genesis and perpetuation of "essential" hypertension"[13]. Potassium depletion is now understood to be a key driver of salt-sensitive hypertension via activation of the thiazide-sensitive sodium chloride cotransporter (NCC) (encoded by *SLC12A3*) in the distal convoluted tubule (DCT)[14–16]. Conversely, potassium loading suppresses NCC-mediated sodium chloride (NaCl) reabsorption, leading to natriuresis and kaliuresis[17–20]. This mechanism — referred to as the K^+ switch — couples dietary potassium intake to renal sodium handling and potassium-mediated blood pressure regulation[21].

Over the past decade, new insights have substantially deepened our understanding of how the kidneys sense and respond to imbalances in dietary potassium and the subsequent effects on the cardiorenal system. However, important questions remain, particularly regarding the optimal daily potassium intake and the ideal reference range for blood potassium that mitigates cardiovascular and kidney disease. Whether these targets should be adjusted based on age, sex, ethnicity or the presence of kidney impairment also remains unclear. In this Review, we explore these issues by examining the physiological determinants of blood potassium levels, the health consequences of chronic hypokalaemia and hyperkalaemia, and the potential benefits of potassium supplementation in the general population and in individuals with CKD. Finally, we discuss strategies to reduce the risk of hyperkalaemia while preserving the protective effects of a potassium-rich diet.

Potassium homeostasis

In adults, total body potassium is around 3,000–4,000 mmol or 55 mmol per kg body weight[22] (Fig. 1a). About 2% of this potassium is extracellular, while 98% is contained within cells, notably those of the muscle and liver, which provide regulated intracellular potassium stores that readily exchange with the extracellular fluid[22]. Given the average intracellular K^+ concentration of 150 mmol/l, this distribution translates to an extracellular K^+ concentration of 4.0 mmol/l.

As extracellular potassium is subject to tight homeostatic control, little variation is seen in the blood concentration. Consistent with electrolyte fluctuations around a specific mean, the physiological range of $[K^+]$ obeys a gaussian distribution[23]. In human populations, this window is generally 3.5–5.0 mmol/l and is maintained by the balance between dietary intake of potassium, redistribution of K^+ between the extracellular and the intracellular fluid, and regulation of potassium excretion by the gut and the kidneys (Fig. 1a). The kidney conserves potassium during times of deprivation and coordinates efficient

kaliuresis following the ingestion of a dietary potassium load. Renal K^+ handling also influences sodium Na^+ reabsorption, so is directly relevant to blood pressure regulation and cardiovascular health.

Kidney potassium sensing and signalling

Following glomerular filtration, potassium is reabsorbed by cells in the proximal tubule and loop of Henle as well as by intercalated cells. Potassium can also be secreted by cells in the late DCT, connecting tubule (CNT) and cortical collecting duct (CCD) — referred to as the aldosterone-sensitive distal nephron (ASDN)[24]. Our understanding of kidney potassium regulation has expanded beyond hormonal control by aldosterone to include direct potassium sensing by the kidney tubule.

Aldosterone

Traditionally, medical textbooks have emphasized the role of the mineralocorticoid hormone aldosterone and collecting duct principal cells in the kaliuretic response[25] (Fig. 1b). This view posits that mammalian potassium sensing is largely carried out by adrenal glomerulosa cells, which release aldosterone in response to a rise in blood potassium concentration. Upon reaching the renal circulation, aldosterone enters principal cells, where it can engage intracellular mineralocorticoid receptors. Subsequent mineralocorticoid receptor-dependent signalling activates the apically expressed epithelial sodium channel (ENaC) (encoded by *SCNN1A*), which transports luminal sodium in filtered tubular fluid. The intracellular movement of sodium generates a lumen-negative transepithelial potential difference, which facilitates the secretion of K^+ down its electrochemical gradient via apically expressed renal outer medullary K^+ channels (ROMK) (encoded by *KCNJ1*). Thus, the kidney can sense and respond to changes in potassium via an indirect mechanism, which relies on the highly K^+ sensitive adrenal gland to activate the potassium secretory machinery of the ASDN[26].

Inwardly rectifying potassium channels

Kidney tubules can also directly sense K^+ through the action of specific inwardly rectifying potassium channels that influence renal potassium handling (Fig. 1b). These channels, which are expressed as heteromeric complexes along the basolateral membrane of kidney tubule epithelia, sample blood potassium concentrations via interactions with the peritubular fluid. In particular, proximal tubule Kir4.2 (encoded by *KCNJ15*) channels and distal nephron Kir4.1 (encoded by *KCNJ10*) channels have been implicated as key basolateral potassium sensors[27–29]. These channels associate with Kir5.1 (encoded by *KCNJ16*) to form heteromeric complexes that exhibit high permeabilities, generating a resting potential that is near the electrochemical equilibrium (Nernst) potential for potassium[27]. Thus, similar to adrenal glomerulosa cells, the basolateral membrane of proximal tubule and distal nephron epithelia functions as a potassium-specific electrode that can 'sense' small fluctuations in extracellular K^+ and translate them into robust effects on membrane voltage that influence cellular responses.

Role of the proximal tubule

The proximal tubule is the major site of sodium reabsorption in the kidney and its ion transport properties are influenced by extracellular potassium (Fig. 1b). Hypokalaemia-induced membrane hyperpolarization via Kir4.2 upregulates the basolateral electrogenic sodium bicarbonate cotransporter 1 (NBCe1) (encoded by *SLC4A4*), which transports Na^+ and HCO^{3-} into the blood. The resulting reduction in cellular pH activates apical sodium hydrogen exchange via the sodium–hydrogen exchanger 3 (NHE3) (encoded by *SLC9A3*).

K^+ depletion also activates intracellular signalling via a Kir4.2-dependent mechanism[30]. Low K^+-induced basolateral membrane hyperpolarization drives the extracellular movement of chloride ions via basolaterally expressed volume-regulated anion channels to maintain electrical balance. The efflux of chloride ions is associated with activation of mammalian target of rapamycin complex 2 and its downstream target kinase Akt, which leads to proximal tubule hypertrophy and expansion[27]. Although secondary chloride efflux seems to be a key factor that dictates this process, the mechanism remains unclear. Nevertheless, current data suggest that hypokalaemia exerts a chloride-dependent trophic effect on the proximal tubule to increase its transport capacity.

Conversely, hyperkalaemia downregulates transcellular sodium transport in the proximal tubule. A rise in potassium concentration reduces K^+ efflux by Kir4.2 channels, and the resulting cellular depolarization suppresses the activity of NBCe1, which results in an increase in intracellular pH. Mathematical modelling indicates that this intracellular alkalinization is critical for inhibition of NHE3 activity[31]. Thus, changes in intracellular pH constitute an important signal that influences the rate of proximal tubule transport activity.

Role of the thick ascending limb

The thick ascending limb (TAL) can absorb K^+ thereby enabling it to be recycled within the medulla. When K^+ levels are elevated, K^+ accumulates in the outer medulla and reduces sodium reabsorption[32]. Thus, the TAL may facilitate potassium-induced natriuresis by increasing the distal delivery of sodium and water[22]. However, the findings of studies of the effects of K^+ on the sodium–potassium chloride cotransporter 2 are inconsistent[22]. These discrepancies may be due to the cellular and functional heterogeneity of the TAL, which contains distinct cell types with variable transporter expression[33,34]. In contrast to other tubular segments, the sensing and signalling mechanisms in the TAL as well as its role during K^+ imbalance remain to be fully elucidated.

Role of the distal convoluted tubule

The DCT is a key potassium-sensing segment of the nephron that regulates K^+ balance[22] (Fig. 1b). During hypokalaemia, Kir4.1-mediated hyperpolarization of the DCT basolateral membrane activates NCC via a kinase-dependent signalling cascade that requires With No Lysine (WNK) kinases[15]. According to the current model, K^+ exit across the basolateral membrane is accompanied by chloride efflux via chloride channel Kb (ClC-Kb) (encoded by *CLCNKB*)[15]. This efflux reduces the intracellular chloride concentration of the DCT, thereby activating WNK4, which is a chloride-sensitive kinase. In turn, WNK4 activates the downstream kinases STE20/SPS1-related proline–alanine-rich kinase (SPAK) and oxidative-stress-responsive kinase 1, which directly phosphorylate NCC at defined sites within its intracellular amino terminus. Once phosphorylated, NCC undergoes a conformational change that facilitates rapid ion flux[35]. However, this putative chloride-dependent process is probably not the only mechanism that contributes to NCC activation during hypokalaemia.

In addition to their role in chloride sensing[36], WNK kinases can sense molecular crowding via the formation of biomolecular condensates — membraneless cytoplasmic foci that concentrate binding partners and amplify signalling[37]. As blood potassium levels decrease, the DCT-expressed WNK pathway forms specialized condensates termed WNK bodies[38]. These signalling assemblies require

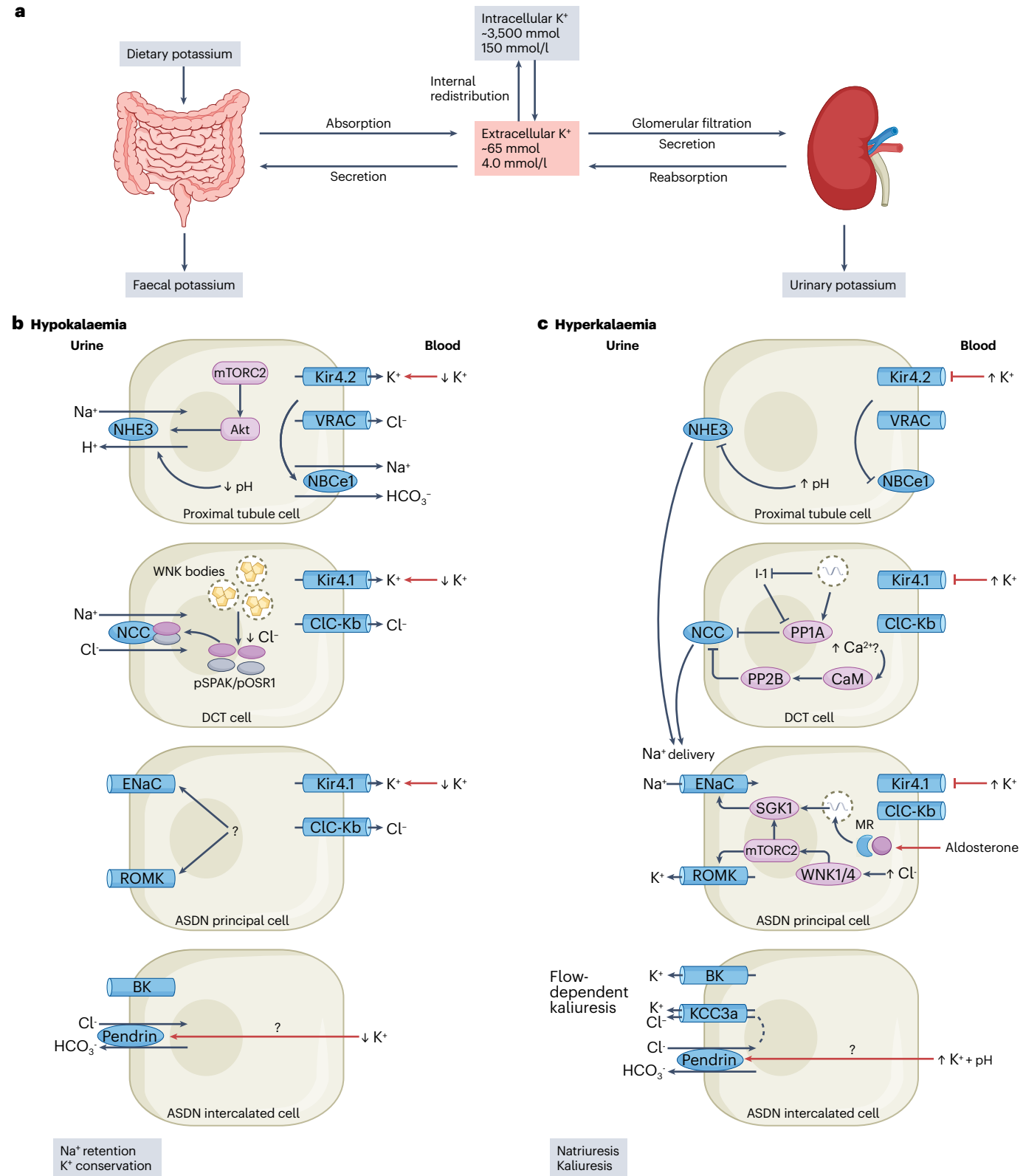
a
Dietary potassium
Intracellular K+
~3,500 mmol
150 mmol/l
Internal redistribution
Absorption
Secretion
Extracellular K+
~65 mmol
4.0 mmol/l
Glomerular filtration
Secretion
Reabsorption
Faecal potassium
Urinary potassium
b Hypokalaemia
Urine
Blood
mTORC2
Kir4.2
K+
↓ K+
Na+
NHE3
Akt
VRAC
Cl-
H+
↓ pH
NBCe1
Na+
HCO3-
Proximal tubule cell
WNK bodies
Kir4.1
K+
↓ K+
Na+
NCC
↓ Cl-
ClC-Kb
Cl-
Cl-
pSPAK/pOSR1
DCT cell
ENaC
Kir4.1
K+
↓ K+
?
ClC-Kb
Cl-
ROMK
ASDN principal cell
BK
Cl-
Pendrin
?
↓ K+
HCO3-
ASDN intercalated cell
Na+ retention
K+ conservation
c Hyperkalaemia
Urine
Blood
Kir4.2
↑ K+
NHE3
VRAC
↑ pH
NBCe1
Proximal tubule cell
I-1
Kir4.1
↑ K+
NCC
PP1A
ClC-Kb
↑ Ca2+?
PP2B
CaM
DCT cell
Na+ delivery
Na+
ENaC
Kir4.1
↑ K+
SGK1
ClC-Kb
MR
mTORC2
Aldosterone
K+
ROMK
WNK1/4
↑ Cl-
ASDN principal cell
Flow-dependent kaliuresis
K+
BK
K+
Cl-
KCC3a
Cl-
Pendrin
?
↑ K+ + pH
HCO3-
ASDN intercalated cell
Natriuresis
Kaliuresis

Fig. 1 | Potassium homeostasis and kidney potassium sensing and signalling. **a**, Potassium (K^+) homeostasis is maintained by adjusting potassium excretion to dietary K^+ intake. Dietary K^+ together with salivary, gastric, pancreatic, biliary and jejunal potassium secretions enter the ileum, where most of the K^+ is absorbed. The remaining K^+ reaches the colon, where additional K^+ secretion and absorption occur. Absorbed K^+ enters the extracellular fluid and is quickly redistributed to the intracellular compartment, where most of the K^+ in the body resides. This process is orchestrated by hormones such as aldosterone, insulin and catecholamines (not shown). Extracellular K^+ also undergoes glomerular filtration and subsequent reabsorption by the kidney tubule. Active secretion of K^+ by the kidney fine-tunes urinary K^+ excretion. Decreased urinary K^+ excretion, as observed in chronic kidney disease, can be compensated for by an increase in faecal K^+ excretion. Gut–kidney kaliuretic signalling may also occur (not shown)[49]. Extracellular K^+ is tightly regulated at approximately 4.0 mmol/l and can be measured in whole blood, plasma or serum. **b**, Effects of hypokalaemia (or lower blood potassium levels within the normal range) on ion transport and intracellular signalling in the proximal tubule, distal convoluted tubule (DCT) and aldosterone-sensitive nephron (ASDN), which comprises principal cells and intercalated cells. The thick ascending limb is not included because the effects of K^+ on this segment have yet to be fully elucidated. The net effect of hypokalaemia is sodium (Na^+) retention and K^+ conservation. Hypokalaemia stimulates potassium chloride secretion through inwardly rectifying potassium channels (Kir) and chloride channels expressed at the basolateral plasma membrane (Kir4.2) and volume-regulated anion channels (VRAC) in the proximal tubule and Kir4.1 and ClC-Kb in the DCT and ASDN. Kir4.2 and Kir4.1 form heteromeric complexes with Kir5.1 (not shown). Whether intercalated cells express Kirs is unclear. Basolateral potassium chloride efflux leads to membrane hyperpolarization. In the proximal tubule, hypokalaemia-induced membrane hyperpolarization activates basolateral sodium bicarbonate cotransporter 1 (NBCe1), which reduces intracellular pH, and in turn activates the apical sodium–hydrogen exchanger 3 (NHE3). Hypokalaemia also activates mammalian target of rapamycin complex 2 (mTORC2) and its downstream target kinase Akt, which enhances proximal tubule hypertrophy and segment expansion[27]. In the DCT, hypokalaemia reduces intracellular [Cl^-] and activates With No Lysine (WNK) kinases, which form specialized condensates termed WNK bodies. WNK bodies phosphorylate the downstream kinases STE20/SPS1-related proline–/alanine rich kinase (SPAK) and oxidative-stress-responsive kinase 1 (OSR), which in turn phosphorylate the sodium chloride cotransporter (NCC), increasing sodium chloride reabsorption. In the ASDN, hypokalaemia results in inhibition of the epithelial sodium channel (ENaC) and the renal outer medullary potassium channel (ROMK) and a reduction in K^+ secretion. The intracellular signalling pathways involved in this process remain unclear. Hypokalaemia also increases the activity of the chloride–bicarbonate exchanger pendrin[18]. **c**, Effects of hyperkalaemia (or higher blood potassium levels within the normal range) on ion transport and intracellular signalling in the proximal tubule, DCT and ASDN. Hyperkalaemia results in natriuresis and kaliuresis. Hyperkalaemia inhibits Kirs and chloride channels and results in membrane depolarization. In the DCT, hyperkalaemia downregulates I-1 expression, which frees PP1A to dephosphorylate NCC, decreasing its activity[44]. K^+ may also inhibit NCC via a calmodulin (CaM) and calcineurin (PP2B or PP3) cascade[175]. Inhibition of NHE3 and NCC increases Na^+ delivery to ENaC for K^+ secretion via ROMK. Increased flow also stimulates flow-dependent kaliuresis via large conductance potassium (BK) channels in intercalated cells. ENaC is also stimulated by hyperkalaemia and aldosterone, which both increase serum and glucocorticoid-regulated kinase 1 (SGK1) activity. Hyperkalaemia activates ENaC probably via effects on intracellular [Cl^-] and subsequent effects on WNK1/4 and mTORC2 (ref. 46). mTORC2 also activates ROMK[176]. A high-K^+ diet also leads to activation of pendrin and the potassium chloride cotransporter 3a (KCC3a), especially with intake of alkaline potassium salts[112]. MR, mineralocorticoid receptor.

kidney-specific WNK1, a truncated DCT-specific isoform that concentrates WNK4, SPAK and other pathway components[39]. A 2025 study showed that WNK bodies are necessary to activate WNK kinases and amplify NCC activity during potassium deficiency[40]. Interestingly, this pathway is activated more efficiently in women than in men, and this activation may have a key role in defending against hypokalaemia during pregnancy[41]. As the efflux of K^+ and chloride across the basolateral membrane is accompanied by water, hypokalaemia may not only lower the intracellular chloride concentration, but also cause cytoplasmic crowding gradients that induce the formation of WNK body condensates[42]. Similar to its effects on the proximal tubule, hypokalaemia is associated with remarkable DCT hypertrophy and length expansion via remodelling[43].

The DCT also expresses enzyme complexes that dephosphorylate NCC during hyperkalaemia, including protein phosphatase 1a (PP1A) and its inhibitory subunit I-1 (encoded by *Ppp1r1a*)[44]. Through unclear mechanisms, hyperkalaemia downregulates I-1 expression and thereby frees PP1A to dephosphorylate its targets, including the N terminus of NCC, which decreases its activity.

Role of the aldosterone-sensitive distal nephron

The ASDN is located downstream of the DCT, includes the CNT and CCD, and comprises principal and intercalated cells. Principal cells express basolateral Kir4.1 channels so are able to sense changes in blood potassium concentrations[29] (Fig. 1b). Direct K^+ sensing in the collecting duct is linked to the apical membrane trafficking of ENaC and ROMK channels; during hyperkalaemia, channel expression is increased at the luminal face to facilitate K^+ secretion[45,46].

Intercalated cells express a dominant basolateral chloride conductance that reflects their resting membrane potential[47]; thus, whether they directly sense changes in blood potassium concentration is unclear. Nevertheless, the intercalated cell is an important participant in potassium homeostasis as it mediates flow-dependent K^+ secretion by apically expressed large conductance potassium (BK) channels[48].

Integrated responses

Through the sensors and signals described above, an increase in blood K^+ after the ingestion of a K^+ load downregulates proximal and DCT sodium transport, shifting Na^+ delivery to the ASDN. Principal cells of the CNT and CCD engage in voltage-dependent K^+ secretion via the actions of ENaC and ROMK, while enhanced flow to the ASDN intercalated cells triggers BK-mediated flow-dependent K^+ secretion (Fig. 1b). The efficiency of these processes is enhanced by direct basolateral K^+ sensing in the ASDN, and by aldosterone release from the adrenal gland. In addition, evidence supports the presence of a gut–kidney kaliuretic pathway that operates independently of blood K^+ levels[49].

By contrast, potassium deficiency activates proximal tubule and DCT-dependent sodium transport[18], switching the site of Na^+ reabsorption to upstream of the ASDN. This process involves direct and rapid augmentation of transporter activity as well as longer-term remodelling and adaptive effects that increase the fractional volume of the proximal tubule and DCT[27,43]. The physiological interaction between K^+ and Na^+ handling serves to conserve potassium during periods of low K^+ intake and to promote kaliuresis during high K^+ intake. This interaction also helps to explain why a low K^+ diet contributes to

salt-sensitive hypertension, whereas a K^+-replete diet exerts natriuretic and antihypertensive effects[22].

Hypokalaemia and hyperkalaemia

As the kidney conserves potassium, healthy individuals will only develop hypokalaemia (blood K^+ <3.5 mmol/l) if they are subjected to extreme potassium deprivation. In a metabolic study in healthy people, blood K^+ concentrations could be driven into the hypokalaemic range if daily potassium intake was reduced to an extremely low level of 1 mmol per day for more than 1 week[50]. By contrast, study participants with a more typical reduced dietary potassium intake of 25 mmol per day remained normokalaemic. In clinical practice, extreme dietary K^+ deficiency is rarely seen other than in severe starvation caused by food scarcity or eating disorders. Even in these settings, additional factors may contribute to potassium imbalance, such as starvation-associated gastrointestinal losses from diarrhoea or inappropriate urinary potassium wasting due to chronic vomiting or hypomagnesaemia. More commonly, patients with typical levels of low dietary K^+ intake become overtly hypokalaemic owing to concomitant illness, medications that cause gastrointestinal losses or medications that induce urinary K^+ losses, such as loop or thiazide diuretics.

Similarly, as the kidney can efficiently excrete a potassium load, high dietary K^+ intake rarely causes hyperkalaemia (defined as blood K^+ >5.0 or 5.5 mmol/l)[51]. In most cases, the pathogenesis of hyperkalaemia requires reduced elimination of K^+ from the kidneys. Such a reduction commonly occurs owing to a chronically reduced glomerular filtration rate (as seen in CKD) but can also be a consequence of impaired K^+ excretion owing to adrenal insufficiency, use of potassium-sparing diuretics (for example, spironolactone and amiloride) or drugs such as trimethoprim or unfractionated heparin, or Mendelian diseases that perturb ion channels, transporters and signalling molecules that regulate renal tubule K^+ handling (for example, Gordon syndrome or Liddle syndrome).

Patients who develop severe hypokalaemia or hyperkalaemia (blood potassium <3.0 or >6.5 mmol/l) exhibit a variety of manifestations, including fatigue and muscle weakness, which in extreme cases can provoke paralysis and cardiac arrhythmias[51]. Those with chronic hyperkalaemia can exhibit adaptation to high blood potassium concentrations that protects against the development of these neuromuscular issues[52], demonstrating that the clinical context in which hyperkalaemia occurs is as important as its severity[53]. Prolonged severe potassium deficiency can lead to chronic changes in the kidney and ultimately fibrosis, termed kaliopenic or hypokalaemic nephropathy.

Hypokalaemic nephropathy

Hypokalaemic nephropathy has been most clearly described in patients with hypokalaemia owing to malnutrition, eating disorders, vomiting, surreptitious use of laxatives or diuretics, or primary aldosteronism[54,55]. Chronic interstitial nephritis and fibrosis have frequently been noted in kidney biopsy samples. WNK bodies[56] and large, irregular cytoplasmic vacuoles in proximal and distal tubule cells, podocytes and arterial myocytes have also been identified in kidney biopsy samples from patients with hypokalaemic nephropathy[57].

As patients with hypokalaemic nephropathy have comorbid conditions, the effects of hypokalaemia are difficult to separate from those of volume depletion and aldosteronism[58]. However, studies in rodents have provided a clearer understanding of the direct effects of K^+ deficiency on the kidney (Fig. 2). These processes begin with the basolateral potassium channel Kir4.2 in the proximal tubule, which facilitates K^+ efflux in response to hypokalaemia[30]. The subsequent intracellular acidosis activates glutaminase and the ammoniagenesis pathway, leading to ammonia production, activation of the alternative complement pathway and the release of cytokines and reactive oxygen species[30,59]. Hypokalaemic nephropathy is also characterized by an ischaemic pattern of injury, with intrarenal angiotensin II generation despite suppression of the systemic RAAS[60]. This ischaemic injury is accompanied by changes in vasoactive mediators, including an increase in endothelin 1 and reductions in kallikrein, nitrite, nitrate and prostaglandin E_2 (ref. 60). Hypokalaemic nephropathy also leads to progressive loss of peritubular capillaries with macrophage infiltration and a reduction in vascular endothelial growth factor and endothelial nitric oxide synthase[61]. Macrophages not only have an important role in propagating hypokalaemic nephropathy, but also respond directly to hypokalaemia by activating WNK–SPAK signalling[62]. Hypokalaemic nephropathy can be prevented by inhibition of Kir4.2, glutaminase, intracellular acidosis, endothelin 1 and macrophage SPAK expression[30,59,62].

Beyond its effects on the proximal tubule, potassium deficiency causes inflammation in the distal nephron[63] and affects transport processes in collecting duct principal cells. Here, potassium deficiency results in rapid downregulation of the water channel aquaporin 2, which leads to arginine vasopressin resistance (nephrogenic diabetes insipidus)[64]. This effect may be due to autophagic degradation of aquaporin 2 (ref. 65) or the conversion of principal cells to A-type intercalated cells, triggered by the suppression of Notch signalling[66]. In a study in healthy men, hypokalaemia induced by a low-potassium diet reduced the maximum urine osmolality from approximately 1,100 mOsm/kg to 300 mOsm/kg, even after administration of exogenous vasopressin, indicating the development of arginine vasopressin resistance[67].

Dietary potassium, blood pressure and cardiovascular risk

Nearly a century ago, Addison reported that potassium was an effective treatment for lowering blood pressure, hypothesizing that hypertension "is in a large part due to a potash poor diet, and excessive use of salt (NaCl)"[68]. Further evidence in support of this hypothesis came from the groundbreaking INTERSALT[69] and Dietary Approach to Stop Hypertension (DASH)[70] studies in the 1980s and 1990s. Estimates based on data from the INTERSALT study suggest that a population-wide increase in dietary potassium intake to the recommended 120 mmol (4.7 g) per day would lower blood pressure and result in an 8–15% reduction in stroke mortality and 6–11% reduction in heart disease mortality[71]. The results of subsequent trials, cohort studies and meta-analyses have provided an overwhelming consensus that increasing dietary potassium intake is associated with decreased cardiovascular risk[72–76]. A meta-analysis of data from 10,709 generally healthy adult participants from six prospective cohorts found that each additional gram of daily urinary potassium excretion is associated with an 18% reduction in cardiovascular risk[75].

Potassium-enriched salt substitutes

Attempts to reduce dietary sodium intake have been largely unsuccessful[77,78], raising the question of whether other population-level, cost-effective dietary interventions could feasibly lower sodium intake and enhance potassium intake (Fig. 3). Four clinical trials have evaluated the impact of potassium-enriched salt substitutes (in which some sodium is replaced by potassium) on blood pressure and cardiovascular outcomes[78–81]. The largest of these was the Salt Substitute and Stroke

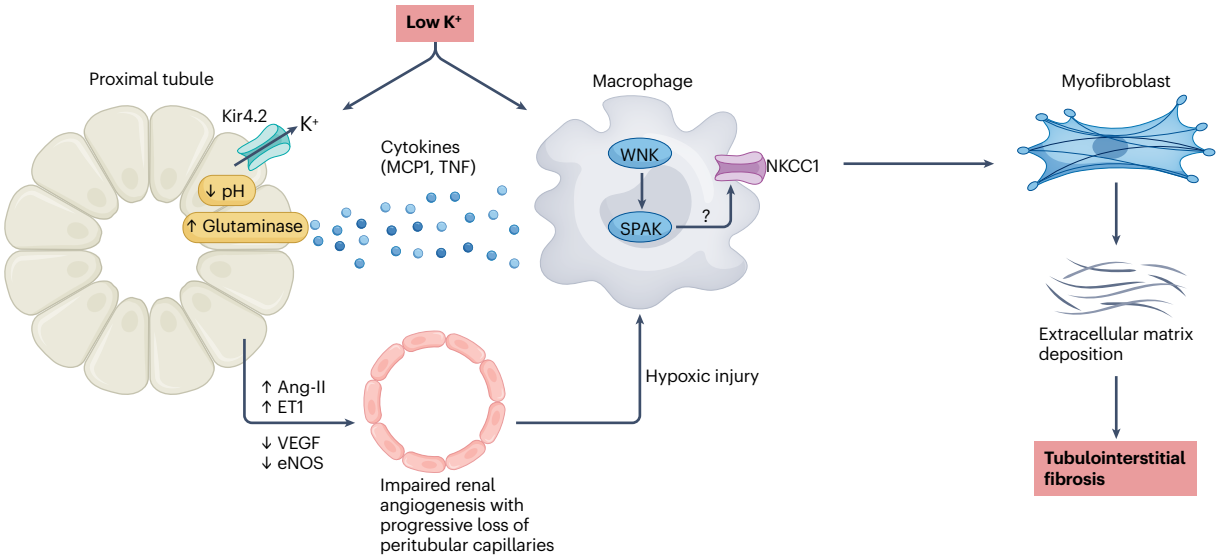

Fig. 2 | Mechanisms of hypokalaemic nephropathy. Hypokalaemia or reductions in blood potassium (K^+) within the normal range (low K^+) can cause kidney injury, inflammation and fibrosis (hypokalaemic nephropathy). In the proximal tubule, hypokalaemia triggers the cellular secretion of K^+ through the inwardly rectifying potassium channel Kir4.2. This secretion reduces intracellular pH and increases the activity of glutaminase, a key enzyme in ammoniagenesis. In turn, activation of ammoniagenesis pathways causes the release of cytokines, including monocyte chemoattractant protein 1 (MCP1), and tumour necrosis factor (TNF)[61], which leads to a cascade of macrophage activation, macrophage transformation into myofibroblasts, deposition of extracellular matrix and the development of tubulointerstitial fibrosis. Macrophages are also directly activated by low K^+, possibly via With No Lysine (WNK) and STE20/SPS1-related proline–alanine rich (SPAK) kinases[62]. The WNK–SPAK kinase pathway activates the sodium–potassium chloride cotransporter 1 (NKCC1) in macrophages, which has a role in clearing apoptotic cells from tissues via efferocytosis[62]. A second pathway of kidney injury involves alterations in vasoactive substances, including decreased levels of vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS), along with increased levels of angiotensin II (Ang-II) and endothelin 1 (ET1)[61]. These alterations lead to impairment of angiogenesis and a progressive loss of peritubular capillaries. The resulting hypoxic injury promotes inflammation and fibrosis through effects on macrophages. In experimental models, hypokalaemic nephropathy can be prevented by inhibition of Kir4.2, glutaminase, intracellular acidosis, ET1, and macrophage SPAK expression (not shown)[30,59,62]. In addition to the proximal tubule, hypokalaemic nephropathy can also affect other segments of the nephron, including the distal tubule and collecting duct[63,64].

Study (SSaSS)[80], in which 20,995 Chinese individuals with a high risk of stroke were randomly assigned to receive either a salt substitute (75% NaCl and 25% potassium chloride (KCl)) or standard salt (100% NaCl). After a mean follow-up of 4.7 years, the salt substitute group exhibited a reduction in systolic blood pressure of 3.34 mmHg as well as a 12–14% reduction in the rate of stroke, major cardiovascular events and death compared with the standard salt group. A subsequent analysis of the SSaSS trial data showed a >99.9% probability that salt substitution would be cost-effective, based on stroke prevention and improvements in quality-adjusted life years[82]. Similarly, the Diet Exercise and Cardiovascular Health (DECIDE)-Salt Trial[78] found that the use of potassium-enriched salt substitutes in facilities caring for older people led to substantial reductions in health-care costs. The researchers projected that rollout of this strategy to all such facilities in China would result in national cost savings of approximately US $55 million within 2 years[83].

A key challenge in interpreting the outcomes of salt substitution trials lies in identifying the relative contributions to blood pressure reduction of reduced sodium intake versus potassium supplementation. Evidence from urinary excretion data suggests that increased potassium intake is the predominant factor that underlies these effects. In the SSaSS trial, participants in the intervention group exhibited a reduction of 8% in urinary sodium and an increase of 57% in urinary potassium excretion[84]. Statistical modelling of the SSaSS urinary data suggested that potassium supplementation accounted for at least 75% of the observed reduction in blood pressure[84]. These findings were corroborated by the DECIDE-Salt Trial, which concluded that salt substitution with KCl is more effective than NaCl restriction alone, which has no significant impact on blood pressure or cardiovascular outcomes[78].

Although potassium supplementation has been shown to save lives, reduce health-care costs and enhance quality of life, the potential risk of hyperkalaemia remains a valid concern[85] (Fig. 3). In the SSaSS trial, a small number of participants with possible hyperkalaemia were identified; however, the incidence was not significantly higher in the salt substitute group than in the standard salt group[80]. This finding may be attributable to the lack of routine measurement of blood potassium levels and/or the exclusion of individuals with known CKD. By contrast, the DECIDE-Salt Trial included a higher-risk population and implemented serial measurements of blood potassium[78]. Although this study found a statistically significant increase in serum potassium levels (0.26 mmol/l) and a corresponding rise in hyperkalaemia risk in the salt substitute group, no adverse clinical outcomes were reported.

A modelling study of individuals with CKD in China estimated that nationwide implementation of potassium-enriched salt substitutes could prevent 32,000 deaths by reducing blood pressure, but might cause 11,000 additional deaths due to hyperkalaemia, resulting in a net decrease of around 21,000 deaths[86]. Similar estimates have been obtained for other countries[87] and a meta-analysis found that the effects of salt substitution on blood pressure are consistent across geographical regions[88].

Optimal potassium intake for cardiovascular health

Despite evidence supporting potassium supplementation in the general and older populations, uncertainties persist regarding the optimal intake. Studies in mouse models have confirmed that potassium deficiency is associated with thiazide-sensitive hypertension[22]. Paradoxically, excessive potassium intake has also been shown to elevate blood pressure in rodents independent of sodium, probably via an aldosterone-dependent mechanism[18,89–92]. A U-shaped relationship between blood potassium levels and blood pressure has also been found in mice[89] (Fig. 4a).

A similar phenomenon has been observed in humans. A meta-analysis of randomized controlled trials reported a U-shaped relationship between potassium supplementation and blood pressure[93] (Fig. 4b), and a meta-analysis of observational cohort studies showed a U-shaped relationship between potassium intake and stroke risk[94] (Fig. 4c). Based on these studies, the researchers suggested an optimal level of potassium intake of 90–130 mmol (3.5–5.1 g) per day[93], which aligns with international guidelines[10,77]. Blood potassium also seems to have a U-shaped relationship with clinical outcomes, with an optimal concentration of 4.0–4.5 mmol/l[95–97] (Fig. 4d). In a clinical trial in patients at high risk of ventricular arrhythmia, a controlled increase in blood potassium levels from 4.0 mmol/l to 4.3 mmol/l (achieved through diet, supplements and/or medication) was associated with fewer arrhythmias, hospitalizations and deaths[98]. U-shaped relationships between blood potassium levels and mortality, as well as cardiovascular outcomes, have also been identified in patients with CKD[96,99–101].

As potassium-enriched salt-substitute initiatives gain attention from governments and the food industry, caution is warranted in vulnerable populations, including those with kidney disease or diabetes, or those who are taking medications that impair potassium excretion.

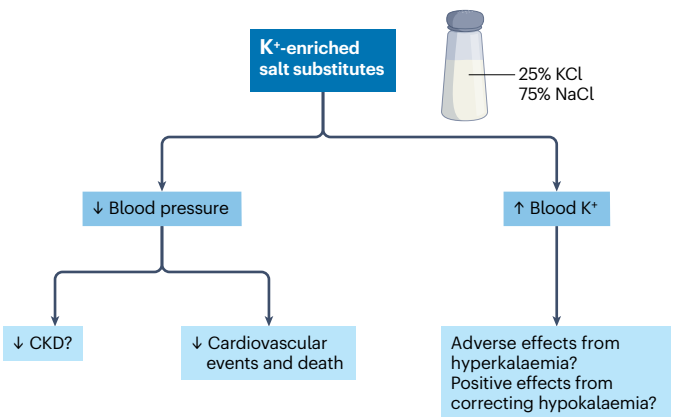

Fig. 3 | Effects of potassium-enriched salt substitutes. Substitution of standard salt with K^+ enriched salt substitutes, which typically contain 25% potassium chloride (KCl), has been shown to lower blood pressure and thereby reduce cardiovascular events and mortality[80]. Observational data suggest that adequate K^+ intake may also attenuate the progression of chronic kidney disease (CKD), but whether this effect is mediated through blood pressure lowering is unclear. The use of K^+-enriched salt substitutes also increases blood K^+ levels. This effect is very modest in the general population (~0.12 mmol/l[119]), but may increase with age, the presence of CKD and the use of medication that can elevate blood potassium levels[120,121]. The net effect of K^+-enriched salt substitutes, especially in individuals with CKD, will depend on the balance between their positive cardiorenal effects and the potential adverse effects of hyperkalaemia.

Demographic factors such as sex and race are also likely to influence the recommendations for potassium intake. Emerging evidence suggests that potassium may exert a particularly protective effect in women and individuals of African descent. Data from the National Health and Nutrition Examination Survey suggest that compared with men, women have lower potassium intake[7], exhibit lower baseline serum potassium[102], are more likely to experience hypokalaemia[102], and derive a greater benefit from increasing potassium consumption[103], especially when on high-sodium diets[74]. Some of these observations may be explained by sexual dimorphism in renal transporters and electrolyte homeostasis[104].

With respect to racial differences, several studies have shown that individuals of African descent tend to have lower blood potassium levels, consume less dietary potassium, and derive disproportionately greater benefit from potassium supplementation than those of other ethnicities[105–108]. These findings underscore the need to investigate population-specific potassium requirements, optimal blood potassium thresholds, and effective strategies for enhancing potassium intake. A critical related question is how an increase in dietary K^+ intake might affect blood potassium levels.

Effect of dietary potassium on blood potassium

The relationship between dietary potassium intake and blood potassium levels is complex and depends on the bioavailability of potassium, the presence of carbohydrates to stimulate insulin secretion and the type of potassium salt present in the food or supplement (Fig. 5). The bioavailability of K^+ in potassium supplements or potassium-enriched salt substitutes is >90%, whereas the bioavailability of K^+ in potassium-rich foods varies from ~50–60% in raw and high-fibre foods to ~90% in processed foods[109]. K^+ is present as potassium citrate or potassium bicarbonate in potassium-rich foods, whereas potassium supplements and potassium-enriched salt substitutes usually contain KCl.

In healthy people, the cellular uptake and urinary excretion of K^+ is greater when K^+ is provided as potassium citrate rather than as KCl[110]. The different behaviour of potassium citrate compared with KCl is explained by contrasting effects on blood pH and plasma aldosterone. An increase in blood pH due to potassium citrate stimulates the NHE in skeletal muscle cells, which subsequently activates the sodium–potassium ATPase pump, driving K^+ into cells[111]. This process is further enhanced by direct activation of the sodium–potassium ATPase by aldosterone.

In a series of physiological studies in mice, potassium bicarbonate was more effective than KCl at stimulating both the electrogenic and electroneutral K^+ secreting mechanisms of the kidney[112]. Enhanced electrogenic K^+ secretion was accompanied by a greater increase in ENaC and ROMK activity, while enhanced electroneutral K^+ secretion resulted from a greater increase in the activity of BK channels, the chloride–bicarbonate exchanger pendrin and the potassium chloride cotransporter 3a (Fig. 1b).

Potassium-rich foods such as fruits and vegetables also contain carbohydrates that stimulate insulin secretion, promoting the shift of potassium into cells and minimizing the increase in blood potassium levels[22,49] (Fig. 5). In a study in healthy individuals and patients with diabetes, inhibition of insulin secretion with somatostatin resulted in an increase in potassium levels without increasing urinary potassium excretion[113]. The high fibre content of fruit and vegetables also helps to promote gastrointestinal potassium excretion by increasing stool frequency, which in turn helps to minimize the effect on blood potassium levels[114]. These kinetics may explain why the relationship between

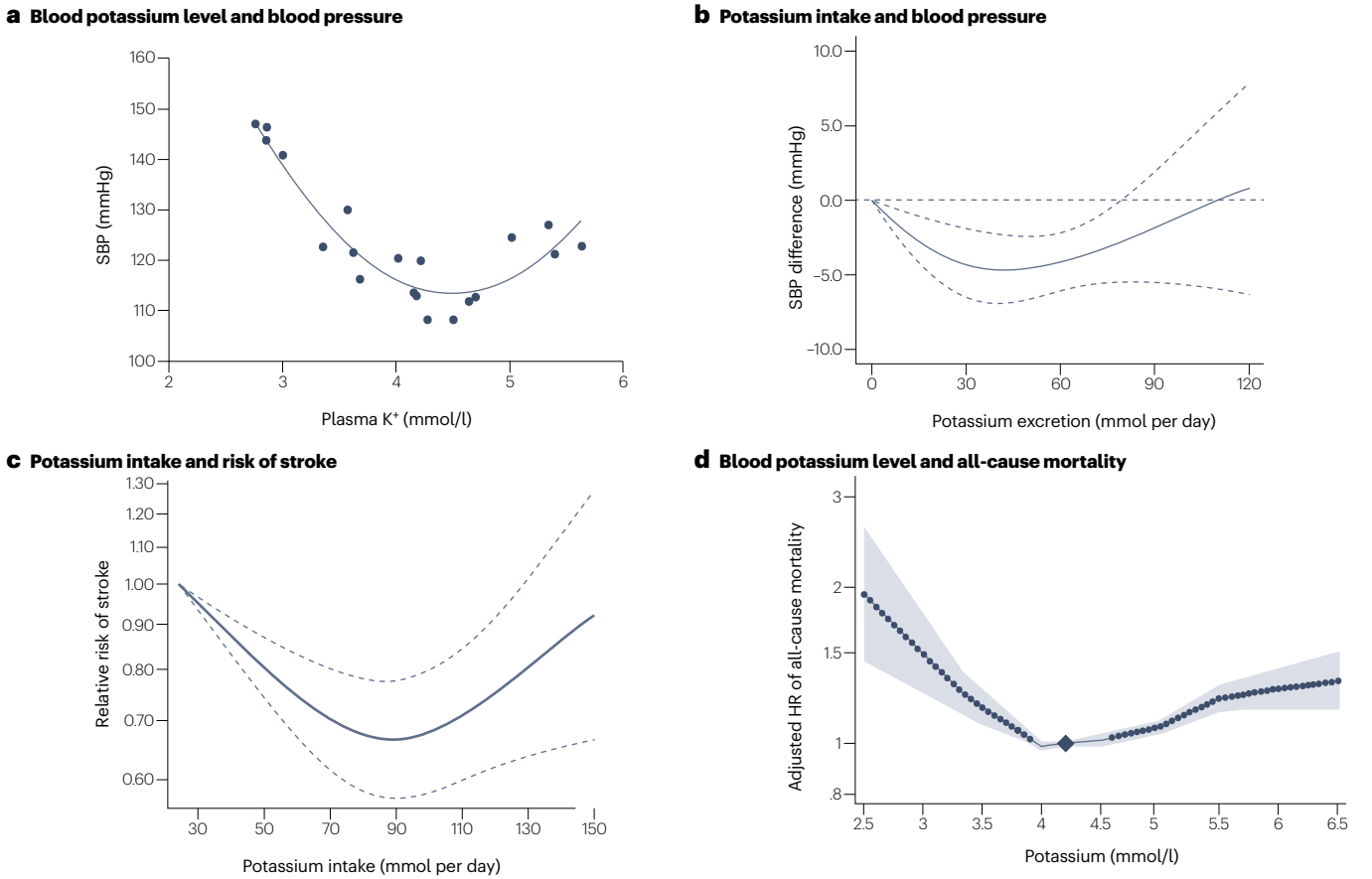

Fig. 4 | Relationships between potassium, blood pressure, risk of stroke and all-cause mortality. a, Relationship between blood potassium levels and systolic blood pressure (SBP) in mice on low-potassium and high-potassium diets[89]. **b**, Relationship between daily potassium excretion (a surrogate measure of potassium intake) and SBP in a dose–response meta-analysis of 32 trials involving potassium supplementation in 1,764 participants, the majority of whom had hypertension[93]. **c**, Relationship between daily potassium intake and risk of stroke in a meta-analysis of 16 studies, which included 19,522 stroke events among 639,440 participants, most of whom had a history of stroke at baseline[94]. **d**, Relationship between blood potassium levels and all-cause mortality in a meta-analysis of 27 general population, high cardiovascular risk and chronic kidney disease cohorts (1,217,986 participants in total)[97]. Part **a** reprinted with permission from ref. 89; part **b** reprinted with permission from ref. 93; part **c** reprinted with permission from ref. 94; part **d** reprinted with permission from ref. 97.

consumption of potassium-rich foods and blood potassium levels is often weak or non-existent, even in individuals with advanced CKD[115–117]. However, an alternative explanation for why studies may not have identified such a relationship is a lack of postprandial blood potassium measurements and the limitations of dietary recalls.

In contrast to fruit and vegetables, potassium supplements or potassium-enriched salt substitutes increase blood potassium levels owing to their high bioavailability and KCl composition (Fig. 5). Systematic reviews have shown that potassium supplements (22–140 mmol/day) increase blood potassium by an average of 0.14 mmol/l[118], whereas potassium-enriched salt substitutes increase blood potassium by 0.12 mmol/l[119].

In a cohort of people aged ≥55 years, underlying disease or reduced kidney function increased the association between dietary K^+ intake and blood K^+ from 0.02 to 0.08 mmol/l for each 10 mmol increase in urinary K^+ excretion (~13 mmol K^+ intake)[120]. Similarly, an observational study in patients with CKD found that the association between urinary and blood K^+ became more pronounced as CKD progressed from stage G3 to G5, increasing from 0.08 to 0.16 mmol/l for each 10 mmol increase in urinary K^+ excretion[121]. These associations are largely consistent with the effects observed in intervention studies involving diet or potassium supplementation. A randomized trial in 29 patients with CKD G3 showed that an increase in dietary K^+ intake from 40 to 100 mmol/day resulted in a 0.21 mmol/l increase in serum K^+ (ref. 122). Similarly, in patients with CKD stage G3b and G4, 40 mmol of K^+ supplementation increased plasma K^+ by 0.4 mmol/l[123]. Together, these studies suggest that increasing dietary potassium intake by 1 g (39 mmol), which is associated with an 18% reduction in cardiovascular risk[75], may raise blood potassium levels by 0.1–0.4 mmol/l, a change that is comparable to the effect of renin–angiotensin inhibitors[124].

Effects of increasing dietary K^+ in CKD

Evidence that adequate dietary potassium intake improves cardiovascular health and has only modest effects on blood potassium levels raises the question of whether such intake might be beneficial in individuals with CKD.

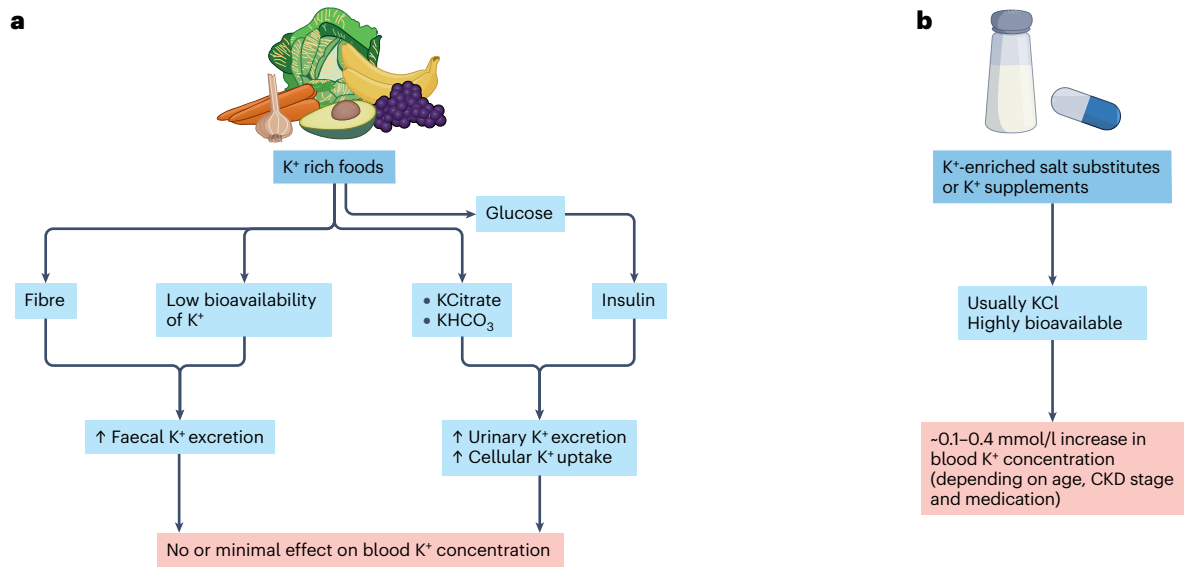

Fig. 5 | Relationship between dietary potassium intake and blood potassium levels. The effect of dietary potassium (K^+) on blood potassium levels ([K^+]) depends on whether the source is K^+-rich foods, K^+-enriched salt substitutes, or K^+ supplements. **a**, K^+-rich foods generally have minimal or no effect on blood K^+ concentration, even in individuals with chronic kidney disease (CKD)[115–117]. Possible explanations include the presence of fibre[114] and the lower bioavailability of K^+ in such foods[109], both of which promote faecal potassium excretion. Furthermore, K^+ in K^+-rich foods is usually present as potassium citrate (KCitrate) or potassium bicarbonate ($KHCO_3$), which stimulate urinary potassium excretion and cellular uptake of potassium[110]. These foods also contain glucose, which stimulates insulin secretion. Insulin facilitates the shift of potassium into cells as well as urinary potassium excretion[49]. **b**, K^+-enriched salt substitutes and K^+ supplements contain potassium chloride (KCl), which is highly bioavailable and can raise blood [K^+]. The magnitude of this effect varies between 0.1 and 0.4 mmol/l and is dependent on factors such as age, CKD stage and use of medication[121–123].

Association with CKD progression

The finding that a low K^+ diet induces hypokalaemic nephropathy in rodents[30,59–62] (Fig. 2), raises the possibility that low dietary K^+ intake could also contribute to progression of human CKD. Several observational studies have investigated the association between urinary K^+ excretion (a proxy for dietary intake) and kidney outcomes (Table 1). In the first study, in 2014, higher urinary K^+ excretion was associated with lower risk of adverse kidney outcomes in patients with high cardiovascular risk[125]. Nine subsequent studies found similar associations[126–134] and in one study, higher urinary K^+ excretion was not associated with kidney outcomes but was associated with improved survival among patients with CKD[135].

By contrast, an analysis of data from the Chronic Renal Insufficiency Cohort (CRIC) found that higher urinary K^+ excretion was associated with faster CKD progression[136]. Notably, CRIC study participants in the lowest quartile of urinary K^+ excretion had poor nutritional status, raising the possibility that loss of muscle mass might have confounded the assessment of estimated glomerular filtration rate (eGFR) and detection of CKD progression. Moreover, an analysis that included self-identified Black participants in the CRIC study found that among those with high-risk *APOL1* alleles, the two highest quartiles of urinary K^+ excretion were associated with a lower risk of CKD progression[137]. By contrast, in those with low-risk *APOL1* alleles, the highest quartile of urinary K^+ excretion was associated with a higher risk of CKD progression. High-risk *APOL1* alleles are a risk factor for CKD progression in African Americans[137] and have been shown to cause cytotoxicity by depleting cellular potassium[138]. These findings raise the possibility that higher dietary K^+ intake might counteract intracellular K^+ depletion owing to the *APOL1* high-risk genotype. Collectively, these studies provided the rationale for an ongoing trial that is investigating the kidney-protective effects of adequate dietary potassium intake in patients with CKD[123].

Blood pressure and kidney function

Increased dietary K^+ intake has been consistently shown to lower blood pressure in individuals with normal kidney function[73]. By contrast, the two intervention studies that investigated the effects of increasing K^+ intake (using diet or supplements) in patients with CKD found no effect on blood pressure[122,123]. This difference may be explained by the meta-analysis finding that taking antihypertensive medication can shift the optimal K^+ intake for blood pressure from 40 to 20 mmol/day[93]. As the participants in the intervention studies received 40 mmol K^+ per day and were using antihypertensive medication, the optimal K^+ intake may have been exceeded, explaining the absence of an antihypertensive effect. Another potential explanation for the lack of blood pressure response to potassium in patients with CKD could be impairment of potassium-induced natriuresis[139]. In a post hoc analysis of a clinical trial in patients with CKD, higher dietary K^+ intake did not affect the antihypertensive effect of the angiotensin receptor blocker losartan, but did reduce the antiproteinuric effect of this drug[140]. This result may be explained by the finding that a high K^+ diet is associated with reduced kidney expression of the type 1 angiotensin receptor[141].

Although the long-term effects of increasing dietary K^+ intake on blood pressure and kidney function in patients with CKD remain to be fully elucidated, rodent studies have provided valuable insights[90]. Rats with CKD induced by five-sixths nephrectomy were more sensitive to a low K^+ diet than healthy controls, exhibiting a greater increase in kidney weight and T cell infiltration. The low K^+ diet also reduced eGFR

and increased albuminuria in the CKD rats. Conversely, a high KCl diet had no effect on blood pressure or kidney function in healthy rats but induced hypertension and kidney collagen deposition without altering eGFR or albuminuria in the five-sixths nephrectomy rats. Notably, a high-potassium citrate diet attenuated the hypertensive effect of the high K^+ diet in these rats. Another study demonstrated that a high alkaline potassium diet improved hypertension following uninephrectomy in rats[142]. Collectively, these findings suggest that in experimental models, a low K^+ diet is directly nephrotoxic with more severe effects in CKD, whereas the effects of a high K^+ diet vary depending on the severity of CKD and the accompanying anion. Several observational studies in humans have also found an increased risk of CKD progression associated with hypokalaemia[96,100,107,143] and hyperkalaemia[97,144].

Dietary K^+ may also affect the gut microbiome and circulating metabolites, which in turn could influence kidney function. In a population-based study, 33 metabolites were found to be associated with dietary K^+, three of which were linked to incident CKD[145].

Potassium binders and other strategies to mitigate hyperkalaemia

In patients with CKD, high-potassium diets and commonly used medications such as RAAS inhibitors and mineralocorticoid receptor antagonists (MRAs) can cause hyperkalaemia, which may limit their use despite their cardiorenal benefits. However, several strategies are emerging to prevent hyperkalaemia and enable patients with CKD to consume high-potassium diets and benefit from continued use of these drugs.

Potassium binders

Sodium polystyrene sulfonate was used as the predominant potassium-binding agent for over 50 years, but safety concerns led to the development of safer, evidence-based alternatives[146,147]. Two novel potassium-binding agents, patiromer and sodium zirconium cyclosilicate (SZC), were approved by the FDA in 2015 and 2018, respectively. Patiromer is a non-absorbable polymer that exchanges calcium for potassium, primarily in the distal colon[148]. By contrast, SZC is an inorganic crystalline compound that exchanges sodium and hydrogen ions for potassium throughout the gastrointestinal tract, including both the small and the large intestines[149].

Patiromer and SZC are particularly useful for the treatment of hyperkalaemia in patients with CKD, heart failure or diabetes, and in those taking RAAS inhibitors and MRAs[150,151] (Fig. 6). Hyperkalaemia often leads to underuse or discontinuation of RAAS inhibitors and MRAs, which are vital to reduce morbidity and mortality in patients with CKD, heart failure and hypertension. Although stopping RAAS

Table 1 | Observational studies of the association between urinary K^+ excretion and kidney outcomes

Study (year)	Population (*n*)	Follow-up	Primary outcome	Finding	Ref.
Smyth et al. (2014)	Patients with high cardiovascular risk and CKD G1–G4 (28,879)	4.5 years	≥30% eGFR decline or dialysis	Highest tertile of U_{K^+} excretion was associated with a lower risk of the primary outcome (OR 0.74, 95% CI 0.67–0.82)	125
Araki et al. (2015)	Patients with T2DM and CKD G1–G2 (623)	11 years	Kidney and cardiovascular events	Higher U_{K^+} excretion was associated with a lower risk of the primary outcome (aHR 0.56, 95% CI 0.33–0.95)	128
He et al. (2016)	Patients with CKD G2–G4 (3,393)	15,807 person-years	≥50% eGFR decline or kidney failure	Highest quartile of U_{K^+} excretion was associated with a higher risk of the primary outcome (HR 1.59, 95% CI 1.25–2.03)	136
Eisenga et al. (2016)	Kidney transplant recipients (705)	3.1 years	Graft failure	Lowest tertile of U_{K^+} excretion was associated with a higher risk of the primary outcome (HR 3.7, 95% CI 1.64–8.34)	127
Nagata et al. (2016)	Patients with T2DM and CKD G1–G3 (1,230)	5.5 years	≥30% eGFR decline or death	Highest and middle tertile of U_{K^+} excretion were associated with lower risk of the primary outcome (HR 0.49, 95% CI 0.28–0.84; HR 0.44, 95% CI 0.22–0.87)	130
Leonberg-Yoo et al. (2017)	Patients with CKD G2–G4 (812)	6.1 years	Kidney failure (KRT)	Higher U_{K^+} excretion was not associated with a lower risk of the primary outcome (aHR 0.95, 95% CI 0.87–1.04)	135
Kim et al. (2019)	Patients with CKD G1–G5 (1,821)	5,325 person-years	≥50% eGFR decline or kidney failure	Lower U_{K^+} excretion was associated with a higher risk of the primary outcome (aHR 1.47, 95% CI 1.01–2.12)	133
Olde Engberink et al. (2020)	Outpatients with CKD G1–G2 (541)	17 years	≥60% eGFR decline, KRT or death	Highest tertile of U_{K^+} excretion was associated with a 76% reduction in the primary outcome	129
Joo et al. (2022)	Adults with CKD G1–G2 (4,088)	37,950 person-years	Incident CKD (eGFR <60 ml/min/1.73 m^2)	Urine Na–K ratio but not U_{K^+} excretion was associated with the primary outcome	132
Ogata et al. (2022)	Outpatients with CKD G3–G5 (240)	4 years	Change in eGFR per year	For each standard deviation increase in U_{K^+} excretion the primary outcome increased by +5.20% (95% CI 2.34–8.14)	126
Kim et al. (2024)	General population (317,612)	11.9 years	Incident CKD	Each standard deviation increase in U_{K^+} excretion was associated with lower risk of the primary outcome (aHR 0.90, 95% CI 0.80–0.92)	131
Suenaga et al. (2025)	Outpatients with CKD G3–G4 (4,314)	5 years	CKD progression (1.5-fold increase in creatinine or kidney failure)	Lowest quartile of U_{K^+} excretion was associated with a higher risk of the primary outcome (HR 1.24, 95% CI 1.03–1.48)	134

aHR, adjusted hazard ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy; T2DM, type 2 diabetes mellitus; U_{K^+}, urinary potassium.

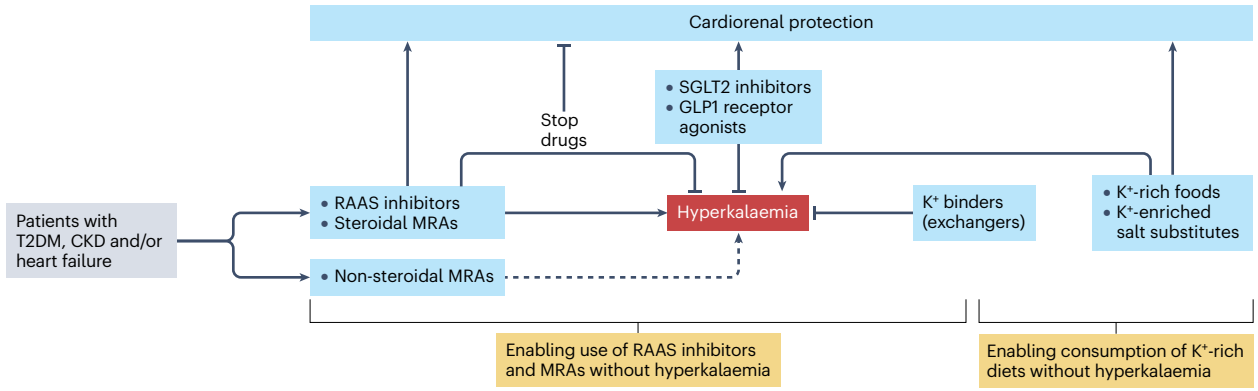

Fig. 6 | Strategies to mitigate hyperkalaemia. Patients with type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD) and/or heart failure are commonly treated with renin–angiotensin aldosterone (RAAS) inhibitors and sometimes with mineralocorticoid receptor antagonists (MRAs), both of which provide cardiorenal protection[109]. However, both RAAS inhibitors and MRAs increase the risk of hyperkalaemia. Several strategies can help to mitigate this risk. First, RAAS inhibitors and MRAs can be discontinued, but this approach is associated with increased cardiovascular mortality[152–154]. Second, using a non-steroidal MRA (for example, finerenone) instead of a steroidal MRA (spironolactone) can reduce — but not eliminate — the risk of hyperkalaemia[171]. Third, concurrent use of glucagon-like peptide 1 (GLP1) receptor agonists or sodium–glucose cotransporter 2 (SGLT2) inhibitors (which also provide cardiorenal protection) has been shown to lower the risk of hyperkalaemia[168]. Fourth, K^+ binders, such as patiromer or sodium zirconium cyclosilicate, may enable continued use of RAAS inhibitors and MRAs without inducing hyperkalaemia[148,155]. However, whether this approach improves long-term outcomes is unclear[160,161]. K^+ binders have also been used to enable patients to consume and benefit from K^+-rich diets without developing hyperkalaemia[165]. However, this approach may blunt K^+-specific health effects and whether K^+ binders prevent postprandial hyperkalaemia is unclear[166].

inhibitors may acutely decrease the risk of hyperkalaemia, long-term discontinuation of these agents is associated with an increase in cardiovascular mortality and major adverse events[152–154]. Both patiromer and SZC have demonstrated efficacy in enabling continuation or re-initiation of RAAS inhibitor and MRA therapy among patients with hyperkalaemia[148,155]. Moreover, two trials demonstrated that the majority of patients with heart failure with reduced ejection fraction can continue and optimize RAAS inhibitor and MRA therapy when used in combination with patiromer or SZC[156,157].

Additional benefits of potassium binders

Although the primary indication for potassium binders is to lower blood potassium, clinical trials have shown several additional benefits (Fig. 6). An exploratory analysis of the OPAL-HK clinical trial found that patiromer significantly decreases serum aldosterone levels, reduces systolic blood pressure, and decreases urine albumin excretion in patients with CKD on RAAS inhibitors[158]. Another analysis of data from three clinical trials found that SZC significantly increases serum bicarbonate levels and decreased serum urea[159]. However, no evidence of a direct effect of potassium binders on robust clinical end points has been reported. A 2024 systematic review and meta-analysis concluded that potassium binders do not have a significant effect on all-cause mortality, although most of the included trials were under-powered with a short duration[160,161].

An interesting question is whether potassium binders might enable patients who are prone to developing hyperkalaemia to consume high-potassium, plant-based diets (such as the Mediterranean diet or the DASH diet), and thereby improve their nutritional status[162] (Fig. 6). Patients with CKD and heart failure are often advised to restrict dietary potassium, which inadvertently limits their intake of fibre, antioxidants and essential minerals. Critically, adherence to plant-based diets is associated with a lower risk of all-cause mortality, both in the general population and among individuals with CKD[163,164]. A feasibility trial found that plant-based diets can be safely introduced in individuals with advanced CKD who are receiving SZC[165]. Future studies with long-term outcomes are required to investigate whether use of potassium binders alters the benefits of a high-potassium diet. Whether potassium binders can prevent postprandial hyperkalaemia also remains unclear[166].

Other strategies to mitigate hyperkalaemia

In addition to potassium binders, several newer pharmacological agents may mitigate the risk of hyperkalaemia and facilitate the use of RAAS inhibitors and MRAs as well as consumption of higher potassium diets in patients with CKD (Fig. 6). These agents include sodium–glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP1) receptor agonists and the non-steroidal MRA finerenone.

A meta-analysis of six randomized controlled trials in patients with type 2 diabetes mellitus (T2DM) at high cardiovascular risk or with CKD, demonstrated that SGLT2 inhibitors significantly reduce the risk of hyperkalaemia without increasing the risk of hypokalaemia[167]. Similarly, a population-based cohort study of adults with T2DM found that treatment with SGLT2 inhibitors or GLP1 receptor agonists is associated with a lower risk of hyperkalaemia compared with use of dipeptidyl peptidase 4 inhibitors[168]. SGLT2 inhibitors are expected to both increase and inhibit urinary K^+ excretion, so how these drugs attenuate the risk of hyperkalaemia while rarely causing hypokalaemia is unclear[169].

GLP1 receptor agonists increase fractional potassium excretion, possibly by inhibiting NHE3 (ref. 170), and may also improve cellular potassium uptake via improved insulin sensitivity. Notably, finerenone is associated with a lower risk of hyperkalaemia and treatment discontinuation than traditional steroidal MRAs such as spironolactone, but a higher risk of these outcomes in comparison with placebo[171]. Collectively, the development of SGLT2 inhibitors, GLP1 receptor agonists and finerenone have helped to overcome hyperkalaemia as a barrier to the

optimal use of therapies providing cardiorenal protection in patients with CKD, T2DM and heart failure.

Conclusions and future directions

The intertwining of kidney K^+ and Na^+ excretion explains why a low-potassium diet can lead to salt-sensitive hypertension, whereas a potassium-replete diet promotes natriuresis and lowers blood pressure. Emerging data suggest that low dietary K^+ intake may also drive CKD progression; however, intervention studies are needed to determine whether this relationship is causal and modifiable through increased dietary K^+ intake. Insights into kidney K^+ sensing and signalling have clarified how hypokalaemia contributes to kidney injury and fibrosis in experimental models. A key question is whether these findings can be translated to humans, as studies in rodent often use extreme dietary interventions involving either complete potassium deficiency or potassium excess. Furthermore, whether hypokalaemia is necessary for this pro-fibrotic effect or if it can be triggered by low blood K^+ levels that are still within the normal range or by low dietary K^+ intake alone, remains to be determined.

Adequate K^+ intake can be leveraged as a dietary strategy to enhance cardiovascular and kidney health. Potassium-enriched salt substitutes can help to increase dietary K^+ intake and are currently recommended by both the WHO[172] and the European Society of Cardiology[173]. However, these guidelines exclude individuals with CKD owing to concerns about hyperkalaemia. Although overt hyperkalaemia should be avoided, whether this concern is justified, particularly in early-stage CKD, is unclear, given that potassium-enriched salt substitutes are expected to increase blood potassium levels to a degree comparable to that caused by RAAS inhibitors[124]. Further research should determine whether the net benefits of potassium-enriched salt substitutes observed in the general population also extend to people with CKD, and to understand how the severity of CKD may affect the risk–benefit ratio[174].

Potassium-rich diets tend to have a smaller impact on blood potassium than potassium-enriched salt substitutes and potassium supplements due to the lower bioavailability of dietary potassium and the potassium-lowering effects of dietary fibre and alkaline potassium salts found in these foods. To promote increased potassium intake while minimizing the risk of hyperkalaemia, additional strategies — such as the use of potassium binders, SGLT2 inhibitors and GLP1 receptor agonists — should be explored in future research. Together, current insights into the role of dietary potassium in cardiovascular and kidney health underscore the need to investigate population-specific potassium requirements, optimal blood potassium thresholds, and effective strategies for enhancing potassium intake.

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